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Re: Comments on 42 CFR 73 **CC:**

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February 11, 2003

Comments on HHS Interim Final Rule on the Possession, Use and Transfer of Select Agents and Toxins, 42 CFR Part 73

(67 FR 76886-76905)

Select Agent Program
Centers for Disease Control and Prevention
1600 Clifton Rd., E-79
Atlanta, GA 30333

Dear Program Director,

The University of Colorado Health Sciences Center submits the following comments on U.S. Department of Health and Human Services' (HHS) Interim Final Rule on the Possession, Use and Transfer of Select Agents and Toxins, 42 CFR Part 73.

As the University is a leading educational and research institution with significant annual external research funding, we believe that the information and suggestions presented here may be valuable to HHS.

The University has not previously been required to register under the current select agent rule (Section 72.6 of Title 42 of the Code of Federal Regulations). In the past, our principal investigators, who perform research using hazardous biological agents and toxins designated as "select agents", have not been required to transfer thesematerials. As the interim final rules address the possession, use, and transfer of select agents and toxins, we have reviewed the rules in detail.

The University understands the concerns of the Administration and Congress and the desire to implement regulations to control the handling, storage, transfer, receipt, use of, and access to select agents. We have also reviewed the comments submitted by Howard Hughes Medical Institute, COGR, AAU and others. You will find that we concur with them on many points.

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Part 73.0 – Applicability

We concur with our colleagues at COGR and others regarding the effective date of the regulations. The February 7, 2003 effective date for the CDC regulations and the February 11, 2003 effective date for APHIS regulations are inconsistent. Since Sections 202(b) and (c) and 213(c) and (d) of the Law provide that the regulations are to become effective 60 days after they are promulgated, and the interim regulations were published in the Federal Register on December 13, 2002, the earliest effective date for both regulations should be February 11, 2003.

73.1 Definitions.

We concur with the HHMI recommendation, regarding inclusion of a definition for "Responsible Official." We concur with using the USDA definition for Responsible Official, which reads, "The individual designated by an entity to act on its behalf. This individual must have the authority and control to ensure compliance with the regulations in this Part."

The use of the terms "area" and "access" are confusing. These words should be defined in this regulation in a clear and precise manner.

We concur with the HHMI recommendation that 42 CFR 73 should include a definition of "access" to mean, "The ability to gain physical control of select agents and toxins."

The rules are confusing because the word "access" is used several times with different meanings. We agree with comments made by the Howard Hughes Medical Institution (HHMI) that the above definition of "access" would minimize uncertainty and help Entities comply with the security, training, and record keeping requirements that rely on "access." The recommended definition would apply to those sections of 42 CFR 73 where "access to a select agent," "access to containers," or "approved for access" are used.

We also agree with HHMI that the term "entry" should replace "access" when a requirement addresses admission to a select agent area by an individual not approved under 73.8. Specifically, "entry" should replace "access" in Sections 73.11(b)(6), 73.13(c) and (e), and 73.14(c)(2). These changes and the above definition would greatly clarify the rules.

Part 73.4 and Part 73.5 HHS Select Agents and Toxins and Overlap Select Agents and Toxins

There are continuing concerns among respected researchers about the inclusion of chemically fragile, small molecule/peptide neurotoxins (tetrodotoxin, saxitoxin, and u-conotoxin), that exhibit limited stability at room temperature.

The issue of chemical fragility is an important one to understand. Conotoxins and agatoxins are, for example, very rapidly degraded in water because they are triple-disulfide bonded polypeptides that require reducing agents (beta mercaptoethanol or dithiothreitol on the bench, glutathione in the organism) to retain their proper folded, disulfide-bonded structure. The disulfide bonds are very readily oxidized and the oxidized toxin molecules have no toxic activity whatsoever.
Indeed, one of our headaches with these toxins is that shipments are sometimes useless because the toxin has become oxidized.

We concur with the HHMI recommendation to delete *Cercopithecine herpesvirus 1* (CHV-1) from the HHS list of select agents and toxins.

We concur with the recommendation that 42 CFR Part 73 include a summary of the risk assessment data that supports the listing of each select agent and toxin as an Appendix to the regulation.

The PL 107-188 calls for a review of these materials by HHS over time. The mechanisms for these reviews need to be addressed.

Part 73.4 para e, Part 73.5 para e regarding Genetic elements, recombinant nucleic acids and recombinant organisms

42 CFR 73.4(e)(1) and 73.5(e)(1) states that "nucleic acids...that can encode infectious and/or replication competent forms of any of the select agent viruses," are covered by the regulations, which thereby excludes replication-incompetent forms. Our recommendation would clarify that this exclusion logically extends to replication-incompetent genetic elements and replication-incompetent recombinant organisms.

We concur with the comments of our colleagues from Rutgers University regarding suggested changes to the language of that paragraph. Provisions in the rule should reflect the current and evolving molecular biology technology. We concur with their comments on section (1) regarding the deletion of the word "viral" and replacing "select agent viruses" with the phrase "select agents." We concur with their comments regarding section (2)

Part 73.8 Security

This provision is written to support responsibilities and functions of the Department of Justice in the implementation of Public Law 107-56 (USA PATRIOT Act) and Public Law 107-188.

This provision does not adequately address many of the details required to promptly obtain security risk assessments. Tthe Department of Justice needs to partner more fully with HHS, CDC and USDA to accomplish their mutual goals. This provision also does not establish an adequate administrative appeals process for individuals to request review of designation as a "restricted person"

The classification of "restricted persons" needs further clarification.

It is unclear to what extent those laboratories, exempt because of minimal quantities of Select Agents toxins, will be impacted by Public Law 107-56 and its implementation. Will the individual researchers working in the laboratories be exempt from Department of Justice regulations?

There is a need to clarify the security risk assessment compliance schedule for new individuals needing access to select agents between June 11, 2003, and November 11, 2003.

Further, we concur with our colleagues from HHMI, University of Wisconsin, and otherswho recommend a 5-year expiration time for the entity certificate and security risk assessments, to simplify the logistics for the entities in submitting the required paperwork.

Part 73.9 Responsible Official

We concur with the comments from our colleague, Dr. David Drummond, University of Wisconsin, regarding explicit language for the Responsible Official to report incidents, and specifically to provide for "whistleblower" protections for the RO.

An entity may appoint an RO from administrative, management or research staff. In any one of these cases, the ability to hold Principal Investigators responsible for the aspects of the regulations requires that the RO have the ability to report in good faith to the proper entity or other officials, any misconduct and any misgivings about conduct, without retribution.

Part 73.10 Safety

The Supplementary Information for this Part in the Federal Register announcement cites the CDC/NIH publications Biosafety in Microbiological and Biomedical

Laboratories, and NIH Guidelines for Research Involving Recombinant DNA Molecules, as providing appropriate guidance to entities in developing and implementing safety plans. CDC further states, "we are seeking comments on the incorporation of these guidelines as requirements."

The Biosafety in Microbiological and Biomedical Laboratories is clearly written as a guidance document and not as a regulation. To incorporate it as a regulation would be a time-consuming process that would impede its usefulness to the biosafety and research communities.

NIH Guidelines for Research Involving Recombinant DNA Molecules is a different type of guidance reference for researchers. It already makes reference to the CDC Biosafety in Microbiological and Biomedical Laboratories and other pertinent documents. It already carries the weight of regulation in its applicability to federally funded scientists, requiring that all recombinant experiments at an institution receiving NIH-funding comply with these regulations.

We concur with the comments from our colleagues at Stanford that HHS use the NIH-RAC for review of proposals utilizing recombinant DNA and Select Agents.

Part 73.11 Security

We appreciate that required Safety and Security Plans are largely performance-based. 42 CFR 73 establishes performance standards and allows our institution to create plans to meet those standards.

We appreciate that the Security requirements of Section 73.11 do not prescribe card access, video surveillance or other specific technologies. Performance-based regulations are most efficient and effective because they allow each Entity to adopt the best compliance methods for its own circumstances and institutional organization. Subsequent changes or additions to the rules should maintain and improve their performance basis.

Recommendation: Clarify that Entities have discretion to define "area" in their security plans.

Entities should have the discretion to define "area" because the appropriate security measures will vary for each location, circumstance and institution. By defining "area" in their security plans, Entities will clearly specify the physical limits of their security measures. A specific delineation of "area" will aid Entities, investigators and inspectors in complying with the rules.

Recommendation: Clarify that 73.11(d)(4) only applies to packages used for the shipment or transfer of select agents or toxins. Also, clarify who should perform these inspections.

It is not practical to inspect the many packages of laboratory supplies, autoclaved waste, etc. that enter and exit the select agent laboratory every day.

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If 73.11(d)(4) applies only to packages used for the shipment or transfer of select agents or toxins, the Responsible Official or the Alternate Responsible Official should perform these inspections.

Part 73.12 Emergency Response

We concur with the HHMI recommendation to revise the first sentence of this provision to read, "An entity subject to the provisions of this Part, must develop and implement an emergency plan that meets the applicable requirements of the OSHA Laboratory Standard, 29 CFR Part 1910, §1910.1450, and the OSHA Emergency Action Plans Standard, 29 CFR Part 1910, §1910.38."

Work conducted with hazardous materials in academic and research institutions is appropriately governed by the OSHA Laboratory Standard, 29 CFR Part 1910, §1910.1450, not by the OSHA Hazardous Waste Operations and Emergency Response Standard, 29 CFR Part 1910, §1910.120, which provides oversight of large scale hazardous materials spill response and remediation. Chemical Hygiene Plans, developed in accordance with the OSHA Laboratory Standard, 29 CFR Part 1910, §1910.1450, address laboratory-scale spill and release procedures. The OSHA Emergency Action Plans Standard, 29 CFR Part 1910, §1910.38 more appropriately addresses an institution-wide emergency response plan.

Part 73.13 Training

We concur with the recommendation of HHMI and otherswhich is to revisethis provision in its entirety to read, "An entity required to register under this Part must provide information and training on safety and security for working with select agents and toxins to each individual approved for access under § 73.8 and each unapproved individual working in or visiting areas where select agents and toxins are handled or stored. An entity may modify the training according to the needs of the individual, the work they will do and their potential exposure. The training need not duplicate training provided under the OSHA Bloodborne Pathogen Standard 29 CFR Part 1910, §1910.1030."

Part 73.14 Transfers

Commercial facilities (i.e. vendors) and professional colleagues will be able to share valuable research tools with recipients that have the authority to use or possess them. They will be required to use the EA101 for all transfers of infectious select agents, and toxins when the quantity is in excess of the exemptions as stated.

However, in the case of a laboratory with exempt quantities of toxins, there is no mechanism described for the vendor or professional colleague to make this determination. It is unclear what will be required in terms of transfer such exempt quantities.

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Is the intention for HHS to monitor all shipments, including exempt quantities of toxins? How does HHS propose this will work? In addition, what will be required for documentation, if the vendor insists on an EA101 to ship exempt quantities, and the time comes when all materials are used up and disposed?

We concur with our colleagues from Sandia National Labs, in their comments regarding the security of materials for inter-entity transfer. The current DOT/IATA regualtions require the complete scientific name to be included in the shipping papers.

COSTS OF IMPLEMENTING THE INTERIM FINAL RULE

We believe the Interim Rule grossly underestimates the cost burden of implementing these new requirements. Implementation of 42 CFR 73 requires that we contemplate the addition of staff, recordkeeping requirements, cyber/information security and training programs, over and above what we can accomplish at this time.

The full cost of implementing this rule will not be known until HHS reviews and approves of individual safety and security plans. Improvements would potentially include expanding electronic card access, alarm systems and security cameras.

As a state institution, we are, along with the other states, facing difficult economic circumstances, and are already under significant budget constraints. It is a conservative estimate that implementation of this regulation will incur a minimum of $60,000 in initial security improvements and upwards of at least $50,000 in additional, ongoing staffing costs.

Conclusion

In conclusion, the University supports the performance-based aspects of these Interim Rules for select agents and toxins. Although the University's select agent activities are moderate, select agents compliance requires the expenditure of significant University resources. We hope that consideration of our comments will facilitate efficient and effective compliance with these new rules.

Sincerely,

Terry L. Howard
Director, Health & Safety

Linda Traylor, Ph.D.
Director, Regulatory Compliance

cc: Dr. John R. Sladek, Jr., Vice Chancellor for Research
Dr. Thomas B. Campbell, MD, Chair, Institutional Biosafety Committee
Dr. Richard Irons, Chair, EHS